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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/825,282	BELLGRAU ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43,45-50 and 54-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-43,45-50 and 54-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/19/07, 12/17/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 03/19/07 has been acknowledged.

Claims 44, 51-53 and 56-63 are canceled.
Claims 64-65 are newly filed.
Claims 1-43, 45-50 and 54-63 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.***

Election/Restrictions

Applicant's election without traverse of Group II, claims 1-43 and 54-55 in the reply filed on 03/19/07 is acknowledged. The applicant further elected "Fas ligand" and "CrmA" as species of interest.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 09/087,195, 08/378,507 and 08/250,478, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (f) he did not himself invent the subject matter sought to be patented.

Claims 1-43 rejected under 35 U.S.C. 102(a) as being anticipated by Shinoura et al (Human Gene Therapy 9(18):2683-2689, 1998, *ref. of record on PTO-1449*).

Shinoura teaches an alternate strategy to use host cells that are resistant to the harmful effect of a pro-apoptotic gene of interest. The cited art teaches a method to propagate a recombinant adenovirus vector comprising nucleic acid encoding Fas-ligand, wherein the method comprises culturing 293 cells transfected with the cowpox virus derived caspase-inhibiting CrmA gene (293-CrmA) and a recombinant adenoviral vector encoding an Fas-ligand (AxCAhFL) see abstract. The cited art teaches generation of a sub line of 293 cells, which contains the coding region of CrmA gene obtained from pcDNA3-CrmA (page 2684, col.1 para.3). The cited art further teaches cDNA encoding human Fas and Fas-ligand (page 2684, col.1 para 4). The cited art further teaches the generation of recombinant adenovirus encoding the Fas-ligand (AxCAhFL) or Fas (AxCAhFas) in 293-CrmA host cells (page 2685, col.2, line 1-3, fig-1). The cited art further teaches the production of recombinant adenovirus (AxCAhFL, AxCAhFas), which results in the expression of Fas-ligand or Fas on the infected target cells (fig-2, fig-3). The nucleic acid of encoding Fas-ligand and CrmA are inherently disclosed by the cited prior art, since the art teaches the nucleic acid construct containing CrmA and Fas-ligand gene sequences. Thus the cited art clearly anticipated the invention as claimed.

Claims 1-43, 45-50 and 54-63 rejected under 35 U.S.C. 102(f) as being anticipated by Hedlund et al (Cell Death and Differentiation 6:155-182, 1999, ref. of record on PTO-1449).

The cited art teaches a method to propagate an adenoviral vector by employing 293 cells that stably express CrmA, a poxvirus inhibitor of apoptosis (page 175, abstract). The cited art teaches the construction of 293-CrmA cells by transfecnting 293 cells with DNA encoding the poxvirus CrmA protein that provide resistance to FasL-mediated apoptosis which increases the efficiency of virus production (page 176, col.1 lines 2-8). The cited art teaches the insertion of cDNA encoding FasL into the E1 region of a replication deficient human adenovirus construct under the control of the CMV promoter (page 176, co.1, para.4). The cited art further teaches the generation of recombinant adenovirus encoding human FasL (Ad-hFasL) using 293-CrmA cells (page 180, col.2, para.2-3). The nucleic acid of encoding Fas-ligand and CrmA are inherently disclosed by the cited prior art, since the art teaches the nucleic acid construct containing CrmA and Fas-ligand gene sequences. In addition the cited art teaches the effect of AD-FasL on prostrate tumor in-vivo (page 178, col.2; page 179 fig-4). Thus given the broadest reasonable interpretation, the cited art clearly anticipated the invention as claimed.

Claim Rejections - 35 USC § 112

Claims *45-50 and 54-63 are* rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature Of Invention:

The instant invention relates to a method for cancer gene therapy.

Breadth Of Claims And Guidance Provided By The Inventor:

The scope of invention as claimed encompasses a method of inducing apoptosis in a cancer cell of a recipient mammal by administering a recombinant viral vector encoding any apoptosis inducing protein. In addition the scope of invention as claimed

further encompasses a method of inducing apoptosis in a cancer cell of a recipient mammal by administering a recombinant viral vector encoding any apoptosis inhibiting protein and any apoptosis inducing protein (see claim 54). At best the specification as filed teaches the construction of recombinant adenovirus encoding FasL and its propagation in 293-CrmA cells (spec. page 69, example-10). The specification further teaches that purified Fas Ligand (protein) suppress T-lymphocyte mediated rejection of transplanted islet cells in diabetic PVC rats (spec. page 60, example-1).

The specification as filed fails to disclose a method of inducing apoptosis in cancer cells of a recipient mammal, by introducing into said mammal (via any and all routes of administration) a recombinant viral vector comprising a) a nucleic acid sequence encoding a protein that inhibits apoptosis and, b) a recombinant viral vector comprising a nucleic acid sequence encoding a protein that induces apoptosis for the prevention of tumor growth and metastases (see claim 54). In addition the specification fails to disclose a method of a method of inducing apoptosis in cancer cells of a recipient mammal by administering a recombinant viral vector (via any and all routes of administration) comprising a nucleic acid sequence encoding a protein that induces apoptosis operatively linked to a transcription control sequence, wherein said recombinant viral vector expresses said protein that induces apoptosis (see claim 64. In addition the specification fails to disclose a method of inducing apoptosis in cancer cells of a recipient mammal, by introducing into the mammal a recombinant viral vector (via any and all routes of administration) comprising any portion of SEQ ID NO:4 and any nucleic acid sequence encoding Fas ligand or a biologically active fragment thereof (see claim 65).

State Of Art And Predictability:

The scope of the instant invention encompasses genetic modification of a cell in-vivo, therefore the invention falls in the realm of gene therapy. The gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. No cures can as yet be attributed to gene therapy (see Goncalves, Bioessays. 27(5):506-517, 2005; Juengst, BMJ, 326:1410-11, 2003; Check NATURE

422:7, 2003; Couzin et al, SCIENCE 307:1028, 2005; Wolf, NAT. BIOTECHNOL. 20, 768-769, 2002, Rosenberg et al, SCIENCE 287:1751, 2000; Anderson, NATURE 392:25-30, 1998; Touchette, NAT. MED. 2(1) 7-8, 1996). Most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. Furthermore, Recombinant DNA Advisory committee (RAC) also emphasized that expectations of current gene therapy protocols have been over sold without any apparent success. The advisory panel further emphasized the need for a greater understanding of an underlying mechanism that contribute the etiology of a disease. For example the etiology of cancer(s) is complex wherein variety of mutated-genes has been implicated in the development of cancer (see Greenman et al, NATURE 446:153-158, 2007), which renders any cancer therapy in general highly unpredictable.

In instant case the art at the time of teaches that Fas system affects human pathology in two ways. The first categories of diseases are characterized by malfunction of Fas-system whereas second category is related to diseases caused by excessive activation of Fas-system (Nagata et al, Science 267:1449-1456, 1995, ref. of record on Pto-1449). Furthermore, Fas is abundantly expressed in liver, heart and lung tissues and injection of anti-Fas monoclonal antibodies in adult mice caused rapid hepatic failure. Therefore, considering the scope of instant invention the systemic administration of a viral vector would leads to the expression of Fas-ligand on any tissue or blood cell type, would certainly lead to Fas/FasL mediated apoptosis in CD4 T-cells, liver cells, heart cells and lung tissues expressing Fas, which would be deleterious to the subject. Therefore, considering the guidance provided in the instant specification it is not clear how one skilled in the art would use the invention as claimed where the Fas is over expressed and the expression of FasL would lead to programmed cell death of cells, tissues and organs expressing the Fas antigen.

Furthermore, one of the greatest challenges facing gene therapy is the efficient transfer and stable expression of transgenes in appropriate tissues. Furthermore, it has been difficult to predict the efficiency and out come of transduced therapeutic genes because various factors govern the expression and/or therapeutic potential of

transduced genes in vivo. The transduction of target cells represents the first critical step in gene therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors. Furthermore, in vitro gene transfer studies are not predictive of in vivo gene therapy because gene transfer frequency is much higher in-vitro models where most of cells are under going rapid cell division, which is quite not the case in-vivo environment. In addition, besides the limitations in gene transfer the problem to selectively target cells in vivo is still one of the most difficult obstacles to overcome. For example, considering the instant specification it is unclear how one skill in the art would selectively target tumor metastases spread to different part of body. The viral particles binds to many cells they encounter in vivo and therefor would be diluted out before reaching their targets. In addition there exists an uncertainty about the degree to which a vector's genetic material may integrate into the host genome extends to most types of gene therapy trials. Scientists are also unsure how an insertion could affect a patient, and worry cancer could occasionally be triggered, such as occurred various trials involving gene therapy. Although, the gene therapy holds much promise to come, the success will only be achieved through continued rigorous research on the most fundamental mechanisms that contribute to a genetic disease along with the pathogenesis of the disease, gene delivery and gene expression in animals.

In instant case treatment of any cancer using a cancer gene therapy approach wherein the genetic vector used comprises any apoptosis inhibiting and/or apoptosis inducing gene of intrest and wherein the vector is administer via any and all routes of administration (i.e. systemic, local, oral, nasal etc) is not considered routine in the art and without sufficient guidance to a specific therapeutic gene and route of administration and the enabled effects the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and limited amount of guidance

provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SUMESH KAUSHAL
PRIMARY EXAMINER